



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 25 1998

Mr. James D. Gustafson
Vice President of Quality Systems
and Regulatory/Clinical Affairs
Possis Medical, Inc.
9055 Evergreen Boulevard, N.W.
Minneapolis, MN 55433-8003

Re: P980017

Possis Perma-Seal® Dialysis Access Graft, Model 2C20

Filed: December 12, 1997

Amended: May 18 and 29, June 3, July 10 and 20, and September 25, 1998

Dear Mr. Gustafson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Possis Perma-Seal® Dialysis Access Graft, Model 2C20-B. This device is indicated for use as a subcutaneous arteriovenous shunt graft to provide immediate and subsequent chronic blood access for high-efficiency hemodialysis in patients who meet one or more of the following conditions:

- central venous cannulation is deemed hazardous or is technically unavailable;
- are being maintained on chronic anticoagulation or antithrombotic therapy; and/or
- are morbidly obese.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 3 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>.

Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

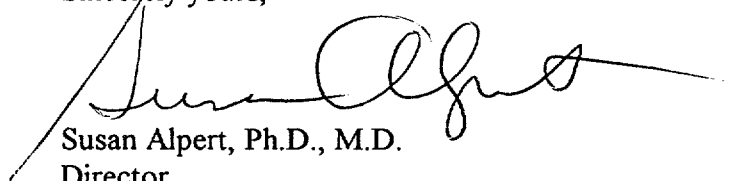
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Dorothy Abel at (301) 443-8262, extension 165.

Sincerely yours,



Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW

Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

Possis Perma-Seal® Dialysis Access Graft

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table of Contents

1	General Information.....	2
2	Indications for Usage.....	2
3	Device Description	2
	Figure 1. Dimensions of The Perma-Seal® Dialysis Access Graft.....	2
4	Contraindications	2
5	Warnings and Precautions	3
6	Adverse Events	3
6.1	Observed Adverse Events:	3
	Table 1. Perma-Seal Graft study summary of all major complications.....	3
6.2	Potential Adverse Events:	4
7	Alternative Practices and Procedures	4
8	Marketing History	4
9	Summary of Preclinical Studies	4
9.1	Bench Testing	4
	Table 2. Physical and functional testing of the Perma-Seal Graft (average \pm SD, range).	5
9.2	Biocompatibility Tests.....	5
	Table 3. Biocompatibility testing for the Perma-Seal Graft.	6
9.3	Animal Testing.....	6
10	Summary of Clinical Studies.....	7
10.1	Objectives	7
10.2	Study Design.....	7
10.3	Description of Patients and Gender Bias	7
	Table 4. Gender of Patients by Study Group.....	7
	Table 5. Hemodialysis Variables by Study Group (Mean \pm SE).....	8
	Figure 2. Actuarial freedom from patency salvage intervention (Kaplan-Meier).....	8
	Table 6. Patency salvage interventions after 30 days	8
	Figure 3. Actuarial freedom from final loss of patency (Kaplan-Meier).....	9
	Figure 4. Actuarial freedom from major complications (Kaplan-Meier).....	9
	Table 7. Major Complications After 30 Days.....	9
	Figure 5. Cumulative distribution of time until first hemodialysis access	10
11	Conclusions Drawn from Studies.....	10
12	Panel Recommendations.....	11
13	FDA Decision	11
14	Approval Specifications.....	11
	Final Draft Labeling (Information for Use)	12
	Approval Order.....	13

Possis Perma-Seal® Dialysis Access Graft

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1 GENERAL INFORMATION

Device Generic Name: vascular graft prosthesis of 6 mm and greater diameter (21 CFR 870.3460).

Device Trade Name: Possis Perma-Seal® Dialysis Access Graft Model 2C20

Applicant's Name and Address:

Possis Medical, Inc.
9055 Evergreen Blvd. NW
Minneapolis, MN 55433-8003

Pre-Market Approval Application (PMA) Number: P980017.

Date of Panel Recommendation: April 23, 1998.

Date of Notice of Approval to the Applicant: SEP 25 1998

2 INDICATIONS FOR USAGE

The Perma-Seal® Dialysis Access Graft is indicated for use as a subcutaneous arteriovenous shunt graft to provide immediate and subsequent chronic blood access for high-efficiency hemodialysis in patients who meet one or more of the following conditions:

- central venous cannulation is deemed hazardous or is technically unavailable;
- are being maintained on chronic anticoagulation or antithrombotic therapy; and/or
- are morbidly obese.

3 DEVICE DESCRIPTION

The Perma-Seal® Graft Model 2C20 (Graft) is constructed of medical grade silicone elastomer and polyester yarn. It is designed to seal after dialysis needle withdrawal. It features a longitudinal orientation line to aid in implant. The Graft has an internal diameter of 6 mm and is supplied with a length of 45 cm.

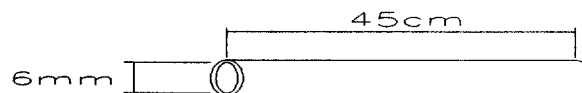


Figure 1. Dimensions of The Perma-Seal® Dialysis Access Graft

4 CONTRAINDICATIONS

None.

8

5 WARNINGS AND PRECAUTIONS

See WARNINGS and PRECAUTIONS in the attached Final Draft Labeling (Information for Use)

6 ADVERSE EVENTS

6.1 OBSERVED ADVERSE EVENTS:

A total of 250 patients were enrolled in the trial, of which 128 received the Perma-Seal Graft and 122 received conventional ePTFE control grafts. A total of 27 of the Perma-Seal Graft patients and 28 of the ePTFE control graft patients died during the study. Causes of death reported for the Perma-Seal Graft patients were sepsis (5), cardiac arrest (4), elective discontinuation of dialysis (3), cardiomyopathy (2), coronary artery disease (2), heart failure (2), and one each of multiple system failure, ruptured gall bladder, intracranial bleeding, and exsanguination through a cut temporary catheter; for five patients the cause of death was unknown. Reported causes of death were similar for the 28 study patients who died after receiving conventional-ePTFE control grafts. The trial defined a major complication as any adverse event which required intervention or any aneurysm or pseudoaneurysm. Table 1 summarizes the major complications reported in the trial.

Table 1. Perma-Seal Graft study summary of all major complications

(Perma-Seal Graft n = 128, 132 pt/yrs follow-up; control n = 122, 138 pt/yrs follow-up)

Complication	Perma-Seal			ePTFE control		
	Total	No. Pts. Reporting	% Pts. Reporting	Total	No. Pts. Reporting	% Pts. Reporting
Aneurysm	7	5	3.9%	1	1	0.8%
Arterial Stenosis	1	1	0.8%	0	0	0.0%
Central Vein Stenosis	1	1	0.8%	0	0	0.0%
Death	27	27	21.1%	28	28	23.0%
Edema	1	1	0.8%	0	0	0.0%
Hematoma	4	4	3.1%	2	2	1.6%
Infection	50	42	32.8%	11	10	8.2%
Kink	1	1	0.8%	0	0	0.0%
Luminal Stenosis	1	1	0.8%	0	0	0.0%
Needle Site Bleed	0	0	0.0%	1	1	0.8%
Perforation of Vein	1	1	0.8%	0	0	0.0%
Pseudoaneurysm	5	3	2.3%	14	11	9.0%
Revision	4	4	3.1%	1	1	0.8%
Skin Erosion	5	5	3.9%	1	1	0.8%
Steal	12	10	7.8%	7	7	5.7%
Thrombectomy	2	2	1.6%	1	1	0.8%
Thrombosis	26	25	19.5%	12	12	9.8%
Other	4	4	3.1%	2	2	1.6%
Any Major Complication	152	84	65.6%	81	42	34.4%

6.2 POTENTIAL ADVERSE EVENTS:

Adverse events (in alphabetical order) potentially associated with the use of the Perma-Seal Graft, including those listed in Table 1, are: aneurysm, arterial stenosis, death, infection, skin erosion, surgical revision, thromboembolism, and thrombosis.

7 ALTERNATIVE PRACTICES AND PROCEDURES

Surgically created arterio-venous fistulas from native vessels is generally considered the most durable long-term access for hemodialysis. If a native fistula cannot be created, conventional ePTFE may be used to create an arterio-venous shunt. These shunts typically require about two weeks to mature before they may first be used for hemoaccess. If the patient requires immediate dialysis, access may be obtained through a central venous catheter placed temporarily through the skin and into a central vein such as the subclavian or jugular vein.

8 MARKETING HISTORY

Perma-Seal Grafts obtained the CE mark in June of 1997 and is marketed in Spain, Italy, and the Netherlands. The Graft has not been removed from any international market for any reason relating to the safety and effectiveness of the device.

9 SUMMARY OF PRECLINICAL STUDIES

9.1 BENCH TESTING

The physical and functional tests performed on the Perma-Seal Dialysis Access Graft are summarized in Table 2. Test results met the acceptance criteria in all cases. Most tests were conducted using the 1994 AAMI Standard for Cardiovascular Implants - Vascular Prostheses, or applicable USP standards.

Table 1. Physical and functional testing of the Perma-Seal Graft (average \pm SD, range).

Parameter	IMPRA Graft (n = 5)	Gore-Tex Graft (n = 3)	Perma-Seal Graft (n = 15)
Inner diameter (mm)	5.88 \pm 0.03 (5.85 - 5.94)	5.87 \pm 0.02 (5.85 - 5.90)	6.06 \pm 0.04 (6.00 - 6.14)
Wall thickness (mm)	0.71 \pm 0.00 (0.71 - 0.71)	0.73 \pm 0.04 (0.68 - 0.78)	1.34 \pm 0.06 (1.25 - 1.41)
Volumetric Porosity (percent)	76.0% 69.2 \pm 2.3	76.0%	58.4 \pm 2.1
Full Length Leakage Test (ml/cm ² •min) (water entry pressure)	NA (31 kPa)	NA (39 kPa)	0.001 \pm .003 NA
Pressurized Burst Strength kilopascals (psi)	353 \pm 53 (276 - 441)	1082 \pm 9 (1069 - 1089)	1261 \pm 90 (1048 - 1392)
Longitudinal Tensile Strength (Newtons)	245 \pm 2.0 (243 - 248)	277 \pm 13.0 (263 - 294)	97 \pm 4.0 (88 - 102)
Circumferential Tensile Strength (Newton/mm)	3.60 \pm 0.30 (3.10 - 4.10)	8.50 \pm 0.70 (7.50 - 9.20)	26.6 \pm 2.1 (22.6 - 30.1)
Longitudinal Suture Retention Strength (g)	332 \pm 23 (297 - 358)	818 \pm 66 (732 - 893)	2823 \pm 415 (1864 - 3602)
Circumferential Suture Retention Strength (g)	955 \pm 78 (866 - 1,054)	966 \pm 122 (865 - 1,158)	1022 \pm 210 (699 - 1390)
Kink Resistance (mm)	15.0 \pm 0.6 (14.0 - 16.0)	15.0 \pm 0.5 (15.0 - 16.0)	27 \pm 1 (26 - 28)
Strength after 15 punctures per cm ² (kilopascals)	257 \pm 22 221 - 290)	322 \pm 65 (276 - 414)	852 \pm 110 (689 - 965)

9.2 BIOCOMPATIBILITY TESTS

Table 2 summarizes the biocompatibility tests recommended in ISO 10993: 1992 for implantable blood contact devices and performed on the Perma-Seal Graft. The Graft passed all screening tests after exposure to all manufacturing process conditions.

Table 2. Biocompatibility testing for the Perma-Seal Graft.

TEST PROTOCOL	TEST SAMPLES
<u>Cytotoxicity</u> : Cultured mouse L929 fibroblast cells exposed to MEM media Graft material extract*.	1 Graft; USP designated control
<u>Hemolysis</u> : Fresh rabbit blood incubated with 10 ml of Graft material extract*, using 0.9% saline media. Adapted from ASTM 756-82 and ASTM 619.	1 Graft; extraction media Graft exposure as control
<u>Physio/Chemical</u> : Buffering capacity, heavy metals, nonvolatile residue, and residue on ignition, per USP XXII, pp. 1572-3.	5 Grafts
<u>Systemic Toxicity</u> : Mice injected with Graft material extracts* using 0.9% saline, USP alcohol, polyethylene glycol, and cottonseed oil media, per USP XXII, pp. 1497-9 and USP -NF, pp. 2703-4 (supp. 5).	20 mice with 4 Grafts; saline control
<u>Intracutaneous Toxicity</u> : Rabbits injected with Graft material extracts* using 0.9% saline, USP alcohol, polyethylene glycol, and cottonseed oil media, per USP XXII, pp. 1497-9 and USP -NF, pp. 2703-4 (supp. 5).	8 rabbits with 4 Grafts; saline control
<u>Carcinogenicity/Genotoxicity</u> : <i>Salmonella typhimurium</i> and mouse L5178Y/TK lymphoma cells exposed to Graft material extracts using 0.9% saline and DMSO media per Ames Salmonella Mutagenicity Assay, and "Health Effects Guideline 476 (Genetic Toxicology: in vitro mammalian cell gene mutation tests), April 1984, published by OECD.	1 Graft; control was extraction media without Graft exposure
<u>Dermal Sensitization</u> : Guinea pigs intradermally injected with Graft material extract using Freund's complete adjuvant media, per Magnusson and Klingman, Allergic Contact Dermatitis, <u>Identification of Contact Allergens</u> , 1970, and USP XXII, pp. 1497-9.	20 Guinea pigs; control was extraction media without Graft exposure
<u>Subchronic Toxicity</u> : Mice dosed 5 days with daily hematology and homeostatic evaluations, and gross necropsy at 14 days, per Page and Sawhney, <u>Proceedings of the Workshop on Subchronic Toxicity Testing</u> , 1980.	20 mice and 2 Grafts; control was extraction media without Graft exposure
<u>Intramuscular Irritant Implant</u> : 90 day intramuscular Graft material implant in rabbits.**	3 rabbits and 4 grafts; USP plastic control
<u>Pyrogens</u> : Material mediated pyrogen testing per USP biological test <151>.	3 rabbits

*Extraction methods per USP <87>, XXII, as recognized by TC 194 (ISO 10993-12).

** Mild foreign body reaction, findings judged unremarkable.

9.3 ANIMAL TESTING

Safety and effectiveness of the Graft were evaluated *in vivo* in a canine femoral arteriovenous shunt model with simulated dialysis access treatments. Biodurability of the Graft was evaluated by tensile strength after explant. The Grafts were punctured as early as nine days after implant, and for up to 75 weeks, with a mean of 47 weeks. Cumulative primary patency was 100% at six months and 80% at one year for both the Perma-Seal Graft and the ePTFE control grafts. In the Perma-Seal Graft canines, two minutes of compression after needle removal fully controlled bleeding in 96% of all puncture pairs, with minimal bleeding in the remaining cases. In the control

12

canines, 46% of all puncture pairs bled after nine minutes of compression, some severely. Explanted Perma-Seal Grafts showed normal tissue capsule, minimal thrombus at puncture sites and no significant intra-Graft stenosis. Subcutaneous implants of three and six months showed retention of strength compared to non-implanted controls.

The *in vivo* animal studies demonstrated that the Perma-Seal Graft is safe and effective and provides enhanced dialysis cannulation site sealing.

10 SUMMARY OF CLINICAL STUDIES

A total of 250 patients requiring AV access grafts were enrolled in a randomized trial comparing the Perma-Seal® Dialysis Access Graft to marketed ePTFE grafts; 128 patients received Grafts, and 122 patients received ePTFE grafts. Average follow-up was 1.1 years.

10.1 OBJECTIVES

The purpose of the randomized trial was to compare the clinical performance of the Perma-Seal Graft to the standard synthetic ePTFE grafts in patients who require blood access for hemodialysis, and to establish the early access option for the Perma-Seal Graft.

10.2 STUDY DESIGN

Patients were randomly assigned with equal probability to implant of either the Perma-Seal Graft or a control ePTFE graft in a multi-center, prospective, randomized, controlled trial.

After initial implantation of either the Perma-Seal Graft or control ePTFE, graft patency and associated complications were recorded at scheduled study follow-up visits and at hemodialysis sessions which utilized the access grafts.

10.3 DESCRIPTION OF PATIENTS AND GENDER BIAS

A total of 250 patients requiring implantation of a hemodialysis access graft and meeting study inclusion/exclusion criteria were enrolled at six US centers between July, 1993 and May, 1997. The mean age of patients was 59 years, and Table 4 shows the gender of patients. Baseline characteristics were similar between study groups (age, gender, race, previous access experience, or medical history). Fifty-one (40%) Perma-Seal Graft patients were cannulated within 10 days, 5 on the same day as implant. None of these patients showed a significant difference in complications or patency salvage when compared to the standard cannulation Perma-Seal Graft patients.

Table 3. Gender of Patients by Study Group

Gender	Perma Seal n=128	Control n=122	Total
<i>Female</i>	69 (28 %)	64 (26%)	133 (53%)
<i>Male</i>	59 (24%)	58 (23%)	117 (47%)
<i>Total</i>	128 (51%)	122 (49%)	250 (100%)

13

For the 250 patients enrolled in the study, the mean age was 59 years, 53% were female and 47% were male. Inclusion criteria, exclusion criteria and study enrollment procedures were designed to avoid gender bias. The 1990 U.S. Renal Data System case mix comprising 1,409 patients reported a fraction of 53% females¹. No important differences in success rate or adverse event rate were detected between males and females in this patient population so the results presented are representative of both genders.

Table 4. Hemodialysis Variables by Study Group (Mean \pm SE)

Variable	Perma-Seal	Control	P-Value
Flow Rate (ml/min)	404.9 (2.9) n = 474	410.8 (3.3) n = 407	0.175
Venous Line Pressure (mmHg)	204.3 (2.0) n = 470	209.9 (2.4) n = 406	0.073
Run Duration (minutes)	182.9 (1.5) n = 474	186.0 (1.8) n = 407	0.199

n = one dialysis record per patient per reported follow-up interval; 250 patients

Primary Patency: Primary patency was measured as the time from graft implant to the first intervention performed to restore lost patency. Figure 2 shows Kaplan-Meier actuarial curves for primary patency for the Perma-Seal and ePTFE control grafts. The Perma-Seal did not perform as well as the control. Table 6 shows that once surgical healing is complete (30 days), the Perma-Seal® Dialysis Access Graft has a rate of 2.8 patency salvage interventions per year, compared to 1.2 per year for the control.

Figure 2. Actuarial freedom from patency salvage intervention (Kaplan-Meier)
Perma-Seal (n = 128) and control ePTFE (n = 122) dialysis access grafts.

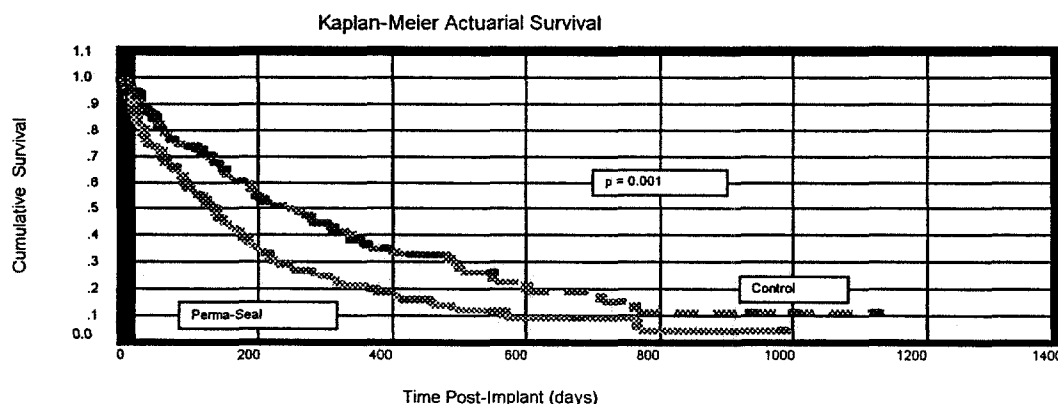


Table 5. Patency salvage interventions after 30 days

Intervention	Perma-Seal	Control	P-Value
No. Events	339	152	
Implant Years	122.0	128.0	< 0.001

¹ Hirth RA, Turenne MN, Woods JD, et. al. Geographic and demographic variations in vascular access. In: Henry ML and Ferguson RM, editors. Vascular access for hemodialysis -- V. W.L. Gore & Associates, Inc., Precept Press, 1997:

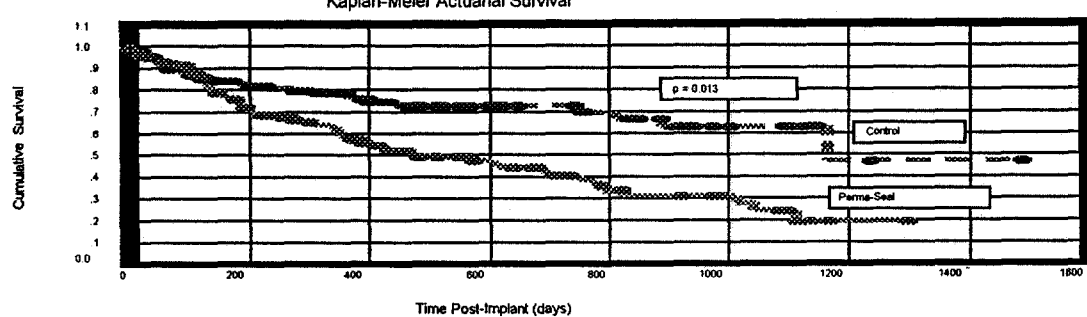
124

Rate (Events/Year)	2.77	1.18	
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Total Patency: The trial measured total patency as the time until final loss of graft function. Figure 3 shows that the total graft life for the Graft was shorter than for the control.

Figure 3. Actuarial freedom from final loss of patency (Kaplan-Meier)

Perma-Seal (n = 128) and control ePTFE (n = 122) dialysis access grafts.



Complications: In the trial, the Graft had a shorter actuarial freedom from major complications than the control, as shown in Figure 4. In addition, Table 7 shows that Graft patients experienced a higher rate of major complications.

Figure 4. Actuarial freedom from major complications (Kaplan-Meier)

Perma-Seal (n = 128) and control ePTFE (n = 122) dialysis access grafts.

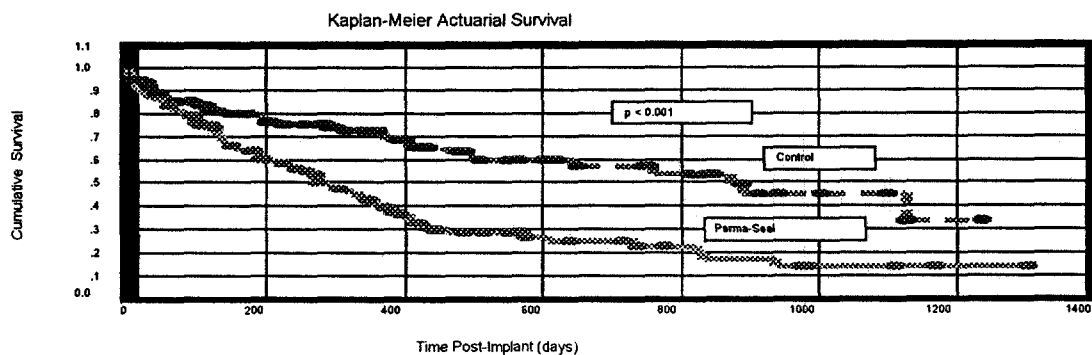


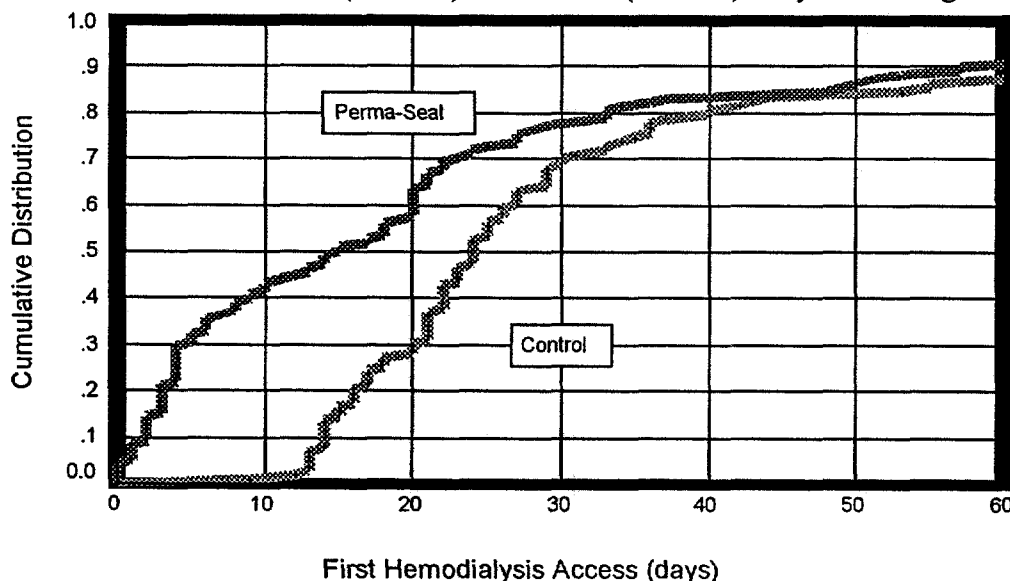
Table 7. Major Complications After 30 Days

Intervention	Perma-Seal	Control	P-Value
No. Events	112	43	< 0.001
Implant Years	122.0	128.0	
Rate (Events/Year)	0.92	0.34	

18

Early Access: About half-way through trial enrollment, patients receiving Grafts were allowed to have first access as soon after surgery as was indicated. Figure 5 shows that over 40% of Graft patients underwent first access within 10 days.

Figure 5. Cumulative distribution of time until first hemodialysis access
for Perma-Seal (n = 118) and ePTFE (n = 103) dialysis access grafts.



11 CONCLUSIONS DRAWN FROM STUDIES

The pre-clinical testing showed that the Perma-Seal Graft is suitable for use in humans, and is able to seal immediately upon dialysis needle withdrawal.

The clinical performance of the Perma-Seal Dialysis Access Graft was evaluated in a randomized trial comparing it to two standard commercially available ePTFE grafts. Trial results included:

- Perma-Seal® Dialysis Access Graft patency was lower than conventional ePTFE AV access grafts.
- Patients receiving the Perma-Seal® Dialysis Access Graft experienced more frequent complications, but the same types of complications, as conventional ePTFE AV access grafts.
- The Perma-Seal® Dialysis Access Graft supported chronic high-efficiency dialysis with flow rates, line pressures, and run times similar to the control.
- The Perma-Seal® Dialysis Access Graft was accessed for dialysis immediately after surgical implantation.
- Early first use did not degrade Perma-Seal® Dialysis Access Graft performance.

The preclinical testing information and the results of the randomized clinical trial provide valid scientific evidence and reasonable assurance that the Perma-Seal Dialysis Access Graft is safe and effective when used in accordance with its labeling.

16

12 PANEL RECOMMENDATIONS

This device was originally submitted as a premarket notification (K972988), and was so presented to the Circulatory Systems Device Panel on April 23, 1998. The Panel recommended clearance of the device for marketing in the U.S. with labeling restrictions as they appear in the Final Draft Labeling (Information for Use) for the device.

13 FDA DECISION

The application was administratively converted to a PMA (P980017) because the INDICATIONS FOR USAGE was new (different from grafts cleared under 510(k)).

FDA concurred with the Circulatory System Devices Panel's recommendation of April 23, 1998, and issued a letter to Possis Medical, Inc. on May 28, 1998, advising that its PMA was approvable subject to the labeling changes recommended by the Panel and required by FDA.

FDA performed an inspection and found the applicant in compliance with the Good Manufacturing Practices (GMP) regulation (21 CFR, Part 820).

14 APPROVAL SPECIFICATIONS

Directions for Use: See Final Draft Labeling (Information for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the labeling.

Post-approval Requirements and Restrictions: See Approval Order

17

Possis Perma-Seal® Dialysis Access Graft

Instructions for Use

Table of Contents

1	Device Description	2
	Figure 1. Dimensions of The Perma-Seal Graft	2
2	Indications for Usage.....	2
3	Contraindications	2
4	Warnings and Precautions	2
4.1	Patient Selection:.....	3
4.2	Sterilization:.....	3
4.3	Precautions during Use:.....	3
5	Adverse Events	3
5.1	Observed Adverse Events:.....	3
	Table 1. Perma-Seal Graft study summary of all major complications.....	4
5.2	Potential Adverse Events:.....	4
6	Clinical Studies	4
	Table 2. Hemodialysis Variables by Study Group (Mean \pm SE).....	5
	Figure 2. Actuarial freedom from patency salvage intervention (Kaplan-Meier)	5
	Table 3. Patency salvage interventions after 30 days.....	5
	Figure 3. Actuarial freedom from final loss of patency (Kaplan-Meier).....	6
	Figure 4. Actuarial freedom from major complications (Kaplan-Meier).....	6
	Table 4. Major Complications After 30 Days.....	6
	Figure 5. Cumulative distribution of time until first hemodialysis access	7
7	Patient Selection and Treatment.....	7
	Figure 6. Orientation of Blood Access Needle.....	7
8	How Supplied.....	8
9	Clinician Use Information	8
	Figure 7. "S" cut at the end of the Graft for end-to-side connection	8
10	Patient Brochure and Labels.....	9

Possis Perma-Seal® Dialysis Access Graft

Instructions for Use

Caution: Federal law restricts this device to sale by or on the order of a physician.

Warning: Long-term Perma-Seal Graft patency is lower and complication frequency higher than for conventional ePTFE grafts. Do not use the Graft in patients in whom native fistulas or conventional ePTFE grafts are able to be used. This device has exhibited more graft infections than conventional ePTFE grafts. The risk of graft infections in patients with cardiovascular prostheses is unknown. Do not use the Perma-Seal Graft as a vascular patch, or for vascular bypass or reconstruction purposes.

1 Device Description

The Perma-Seal® Graft Model 2C20 (Graft) is constructed of medical grade silicone elastomer and polyester yarn. It is designed to seal after dialysis needle withdrawal. It features a longitudinal orientation line to aid in implant. The Graft has an internal diameter of 6 mm and is supplied with a length of 45 cm.

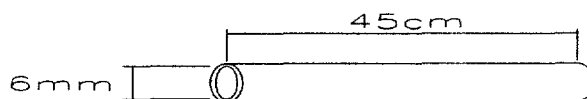


Figure 1. Dimensions of The Perma-Seal Graft

2 Indications for Usage

The Perma-Seal® Graft is indicated for use as a subcutaneous arteriovenous shunt graft to provide immediate and subsequent chronic blood access for high-efficiency hemodialysis in patients who meet one or more of the following conditions:

- central venous cannulation is deemed hazardous or is technically unavailable;
- are being maintained on chronic anticoagulation or antithrombotic therapy; and/or
- are morbidly obese.

3 Contraindications

None

4 Warnings and Precautions

- This device should be used only by physicians trained in vascular surgery techniques, who have training or experience in the use of dialysis access grafts, at facilities adequate for the conduct of such surgery. The device should be used only by physicians prepared to provide long-term follow-up patient monitoring.

4.1 Patient Selection:

- Long-term Perma-Seal Graft patency is lower and complication frequency higher than for conventional ePTFE grafts. Do not use the Graft in patients in whom native fistulas or conventional ePTFE grafts are able to be used.
- This device has exhibited more graft infections than conventional ePTFE grafts. The risk of graft infections in patients with cardiovascular prostheses is unknown.
- Do not use the Graft as a vascular patch, or for vascular bypass or reconstruction purposes.

4.2 Sterilization:

- The Perma-Seal Graft is intended for single use only. Do not resterilize or reuse.
- Inspect sealed sterile package before opening. Do not use if seal is broken: contents may not be sterile and may cause infection in the patient.

4.3 Precautions during Use:

- Do not stretch the Perma-Seal Graft during surgical handling and implantation. Implant the Graft in a relaxed condition. Advance the Graft slowly using the tunneler (at a rate less than 10 cm per second) avoiding elongation or tension.
- Prophylactic antibiotics should be employed in the perioperative period. It is recommended that perioperative antibiotic drip, irrigation of the surgical wound(s) with antibiotic solution, and appropriate pre- and post-operative antibiotic regimen be included.

5 Adverse Events

5.1 Observed Adverse Events:

A total of 250 patients were enrolled in the trial, of which 128 received the Perma-Seal Graft and 122 received conventional ePTFE control grafts. A total of 27 of the Perma-Seal Graft patients and 28 of the ePTFE control graft patients died during the study. Causes of death reported for the Perma-Seal Graft patients were sepsis (5), cardiac arrest (4), elective discontinuation of dialysis (3), cardiomyopathy (2), coronary artery disease (2), heart failure (2), and one each of multiple system failure, ruptured gall bladder, intracranial bleeding, and exsanguination through a cut temporary catheter; for five patients the cause of death was unknown. Reported causes of death were similar for the 28 study patients who died after receiving conventional ePTFE control grafts. The trial defined a major complication as any adverse event which required intervention or any aneurysm or pseudoaneurysm. Table 1 summarizes the major complications reported in the trial.

Table 1. Perma-Seal Graft study summary of all major complications
(Perma-Seal Graft n = 128, 132 pt/yr follow-up; control n = 122, 138 pt/yr follow-up)

Complication	Perma-Seal			ePTFE control		
	Total	No. Pts. Reporting	% Pts. Reporting	Total	No. Pts. Reporting	% Pts. Reporting
Aneurysm	7	5	3.9%	1	1	0.8%
Arterial Stenosis	1	1	0.8%	0	0	0.0%
Central Vein Stenosis	1	1	0.8%	0	0	0.0%
Death	27	27	21.1%	28	28	23.0%
Edema	1	1	0.8%	0	0	0.0%
Hematoma	4	4	3.1%	2	2	1.6%
Infection	50	42	32.8%	11	10	8.2%
Kink	1	1	0.8%	0	0	0.0%
Luminal Stenosis	1	1	0.8%	0	0	0.0%
Needle Site Bleed	0	0	0.0%	1	1	0.8%
Perforation of Vein	1	1	0.8%	0	0	0.0%
Pseudoaneurysm	5	3	2.3%	14	11	9.0%
Revision	4	4	3.1%	1	1	0.8%
Skin Erosion	5	5	3.9%	1	1	0.8%
Steal	12	10	7.8%	7	7	5.7%
Thrombectomy	2	2	1.6%	1	1	0.8%
Thrombosis	26	25	19.5%	12	12	9.8%
Other	4	4	3.1%	2	2	1.6%
Any Major Complication	152	84	65.6%	81	42	34.4%

5.2 Potential Adverse Events:

Adverse events (in alphabetical order) potentially associated with the use of the Perma-Seal Graft, including those listed in Table 1, are: aneurysm, arterial stenosis, death, infection, skin erosion, surgical revision, thromboembolism, and thrombosis.

6 Clinical Studies

A total of 250 patients requiring AV access grafts were enrolled in a randomized trial comparing the Perma-Seal Graft to marketed ePTFE grafts; 128 patients received Grafts, and 122 patients received ePTFE grafts. Average follow-up was 1.1 years. Based on this study:

- Perma-Seal Graft patency is lower than conventional ePTFE AV access grafts.
- Patients receiving the Graft experience more frequent complications, but the same types of complications, as conventional ePTFE AV access grafts.
- The Graft supports chronic high-efficiency dialysis.
- The Graft may be accessed for dialysis immediately after surgical implantation.
- Early first access does not degrade Graft performance.

Support of Chronic Dialysis: The Perma-Seal Graft supported chronic, high-efficiency dialysis, with flow rates, line pressures, and run times similar to the control, as shown in Table 2.

Table 2. Hemodialysis Variables by Study Group (Mean \pm SE)

Variable	Perma-Seal	Control	P-Value
Flow Rate (ml/min)	404.9 (2.9) n = 474	410.8 (3.3) n = 407	0.175
Venous Line Pressure (mmHg)	204.3 (2.0) n = 470	209.9 (2.4) n = 406	0.073
Run Duration (minutes)	182.9 (1.5) n = 474	186.0 (1.8) n = 407	0.199

n = one dialysis record per patient per reported follow-up interval; 250 patients

Primary Patency: Primary patency was measured as the time from graft implant to the first intervention performed to restore lost patency. Figure 2 shows Kaplan-Meier actuarial curves for primary patency for the Perma-Seal Graft and ePTFE control grafts. The Graft did not perform as well as the control. Table 3 shows that once surgical healing is complete (30 days), the Graft has a rate of 2.8 patency salvage interventions per year, compared to 1.2 per year for the control.

Figure 2. Actuarial freedom from patency salvage intervention (Kaplan-Meier)
Perma-Seal Graft (n=128) and control ePTFE (n=122) dialysis access grafts.

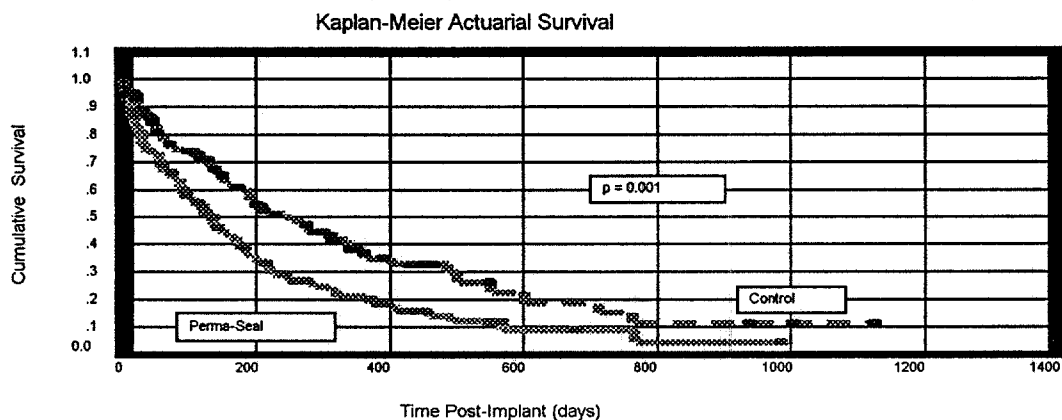


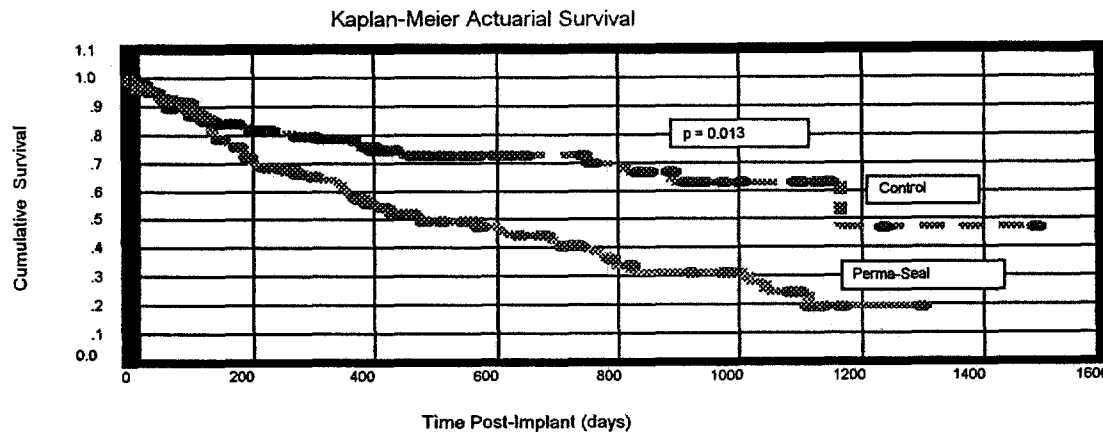
Table 3. Patency salvage interventions after 30 days

Intervention	Perma-Seal	Control	P-Value
No. Events	339	152	< 0.001
Implant Years	122.0	128.0	
Rate (Events/Year)	2.77	1.18	

Total Patency: the trial measured total patency as the time until final loss of graft function. Figure 3 shows that the total graft life for the Perma-Seal Graft was shorter than for the control.

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Figure 3. Actuarial freedom from final loss of patency (Kaplan-Meier)
Perma-Seal Graft (n=128) and control ePTFE (n=122) dialysis access grafts.



Complications: In the trial, the Perma-Seal Graft had a shorter actuarial freedom from major complications than the control, as shown in Figure 4. In addition, Table 4 shows that Graft patients experienced a higher rate of major complications.

Figure 4. Actuarial freedom from major complications (Kaplan-Meier)
Perma-Seal Graft (n=128) and control ePTFE (n=122) dialysis access grafts.

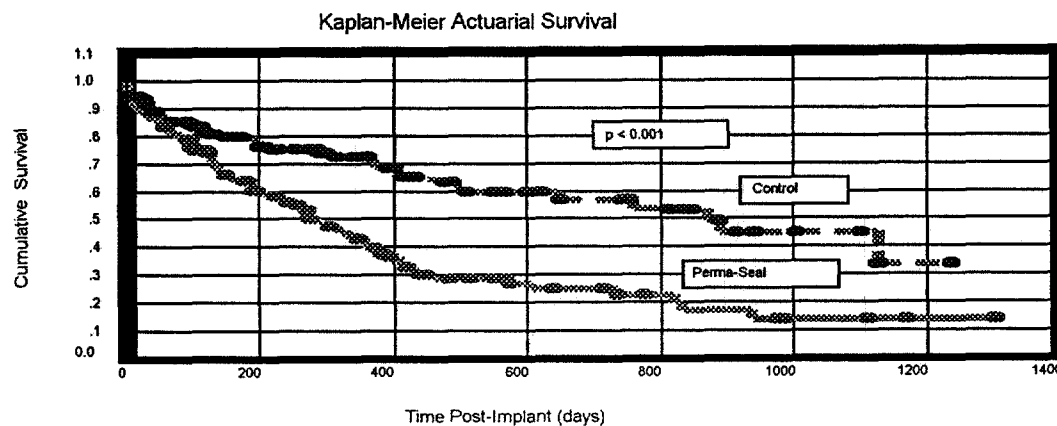
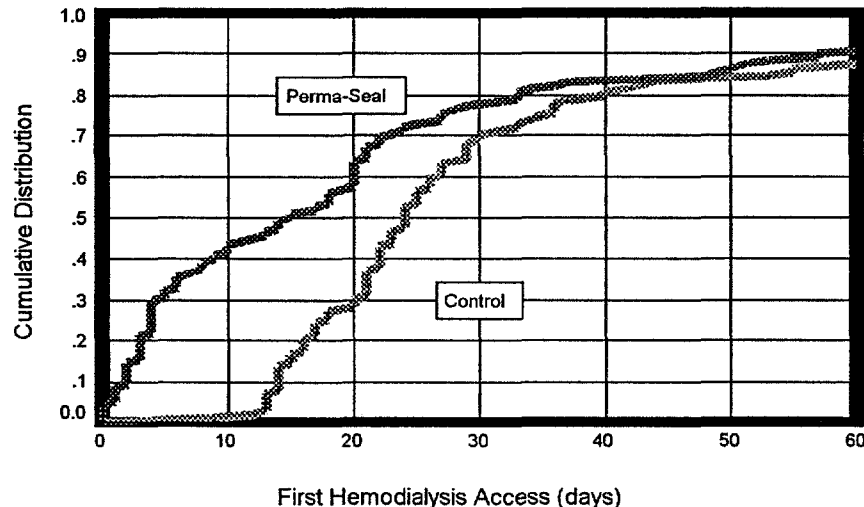


Table 4. Major Complications After 30 Days

Intervention	Perma-Seal	Control	P-Value
No. Events	112	43	
Implant Years	122.0	128.0	
Rate (Events/Year)	0.92	0.34	< 0.001

Early Access: About half-way through trial enrollment, patients receiving Perma-Seal Grafts were allowed to have first access as soon after surgery as was indicated. Figure 5 shows that over 40% of Graft patients underwent first access within 10 days.

Figure 5. Cumulative distribution of time until first hemodialysis access
for Perma-Seal Graft (n = 118) and ePTFE (n = 103) dialysis access grafts.



7 Patient Selection and Treatment

As with any dialysis graft, patients should be carefully monitored when using the Perma-Seal Graft. Graft function may be monitored through standard clinical and imaging techniques, except that the Graft is opaque to ultrasonography.

During routine hemodialysis, rotate the puncture sites to avoid localized damage to the Graft wall. Puncture sites must be adequately separated when repeated needle punctures of the Graft are necessary. Multiple punctures in the same area may lead to disruption of the Graft material or formation of a perigraft hematoma or pseudoaneurysm.

The blood access needle should be inserted at approximately a 45° angle with the bevel up until the Graft is penetrated (see Figure 6). Rotate the needle so that the bevel is down and advance it parallel to the Graft. Inserting the needle at an angle which is too small between the needle axis and the Graft, could tear the wall of the Graft. Inserting the needle at a 90° angle, could puncture the far wall of the Graft.

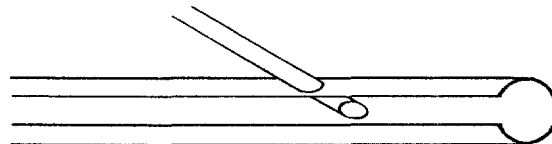


Figure 6. Orientation of Blood Access Needle

In the event of Graft occlusion, the Graft can be declotted with a Fogarty®-type thrombectomy catheter. If a longitudinal Graft incision is used, pre-place stitches before introducing the embolectomy catheter. If a transverse incision is used, pre-placed horizontal mattress stitch is recommended. The pre-placed stitches will

aid in closure. Follow the catheter manufacturer's instructions regarding balloon size and inflation. Do not place undue stress on the anastomoses or incision when placing or removing the catheter. Thrombolysis urokinase may also be used, following standard techniques.

The physician or other care-giver should review the Patient Manual with the patient.

8 How Supplied

The Perma-Seal Graft is supplied sterile. Sterility may be compromised if the package is opened or damaged. The storage life of the Graft is three years from the date of sterilization.

9 Clinician Use Information

1. Open the sterile package using standard sterile technique.
2. The Perma-Seal Graft does not require preclotting. Contact with organic solvents such as alcohol should be avoided. Hemostatic agents may be applied to complete Graft anastomoses or help in minimizing any bleeding that may occur.
3. When implanting the Graft, take care to determine the proper length to allow adequate placement to eliminate excessive stress on the anastomoses and to minimize kinking. Cut the Graft with a sharp surgical instrument, edges should be carefully trimmed.
4. Create a subcutaneous tunnel that approximates the Graft diameter to avoid delayed or insufficient perigraft tissue attachment contributing to perigraft seroma. Dilate using a tunneler with an outer sheath through which the Graft can be pulled without excessive friction to allow a snug fit and minimize subcutaneous bleeding.
5. Use the longitudinal orientation line on the Graft throughout construction of the anastomoses to avoid twisting or torquing of the Graft.
6. Use an appropriate anastomotic angle to minimize undue stresses which may lead to mechanical disruptions of the Graft, host vessel and/or suture lines. For an end-to-side connection, best results may be achieved by fashioning an "S" cut at the end of the Graft (see Figure 7).



Figure 7. "S" cut at the end of the Graft for end-to-side connection

7. Best results are obtained using a small diameter non-cutting tapered needle with a non-absorbable 5.0 or 6.0 monofilament suture, approximately the same size as the needle to minimize bleeding from the suture holes. Do not use a full radius cutting needle as it may damage the Graft at the suture line. Care should be taken to follow the curve of the needle to minimize suture hole elongation. When placing a suture, avoid excessive tension on the suture line and incorporate sufficient material in the stitch. Use an appropriate Graft length. Excessive anastomotic bleeding may occur if excessive tension causes suture

holes to elongate or tear, if the needle-to-suture diameter is too great, or if gaps occur between the Graft and host vessels.

8. If intra-procedural angiography is performed, use the proximal artery for injection whenever possible.

10 Patient Brochure and Labels

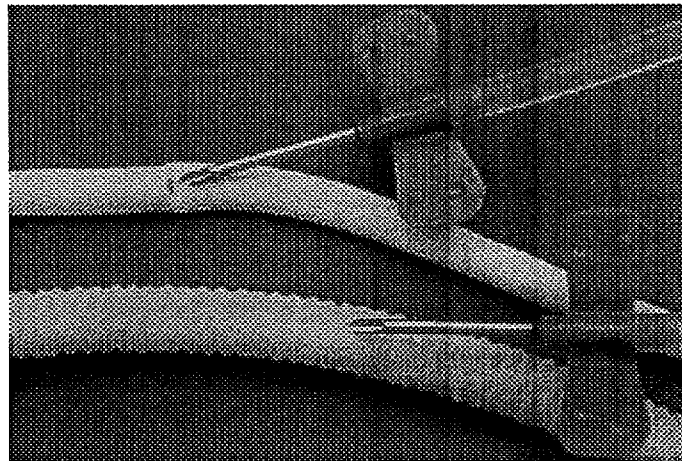
A Patient Education Brochure is enclosed with the Perma-Seal Graft. Additional copies are available from Possis Medical, Inc.

Labels have been supplied for patient records. Please take time to fill out the Graft Implant Registration Form completely and return it to Possis Medical, Inc.



Possis Perma-Seal® Dialysis Access Graft

Patient Education Brochure



Perma-Seal® is a registered trademark of Possis Medical, Inc.

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Manufacturer's Official EU Representative:
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• 1015 CS Amsterdam • The Netherlands
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Caution: Federal law restricts this device to sale by or on the order of a physician.

27

Dear Dialysis Patient:

Your physician has determined that you may benefit from receiving the Possis Perma-Seal® Dialysis Access Graft to support your need for blood dialysis.

This brochure will help you understand the Perma-Seal Graft and its use. If you have questions after reading it, be sure to ask your physician or nurse.

Your physician or nurse will also help you understand your need for dialysis, and the surgery used for implanting devices like the Perma-Seal Graft.

Indications for Use:

The Perma-Seal Graft is indicated for use as a subcutaneous arteriovenous shunt graft to provide immediate and subsequent chronic blood access for high-efficiency hemodialysis in patients who meet one or more of the following conditions:

- central venous cannulation is deemed hazardous or is technically unavailable;
- are being maintained on chronic anticoagulation or antithrombotic therapy; and/or
- are morbidly obese.

Warning: Long-term Perma-Seal Graft patency is lower and complication frequency higher than for conventional ePTFE grafts. Do not use the Graft in patients in whom native fistulas or conventional ePTFE grafts are able to be used. This device has exhibited more graft infections than conventional ePTFE grafts. The risk of graft infections in patients with cardiovascular prostheses is unknown. Do not use the Perma-Seal Graft as a vascular patch, or for vascular bypass or reconstruction purposes.

The Possis Perma-Seal® Dialysis Access Graft

The Perma-Seal Graft is surgically implanted beneath your skin to provide easy access for blood to be drawn out for dialysis and then returned to your body. This graft links an artery to a vein, providing a wide pathway for rapid blood flow to support dialysis.

Such implants are called arterio-venous access grafts, or AV access grafts for short. AV access grafts are usually implanted in the forearm, but sometimes also in the upper arm, leg or other area. Figure 1 diagrams a common surgical lay-out of an AV access graft in the forearm, and its connection to a natural artery and vein.



Figure 1.

This operation is very common. More than 60% of the people in America who receive long-term dialysis have implanted AV access grafts. Although these grafts have complications such as blockages or infections which must be corrected before they can be used again for dialysis access, they are a means to support long-term dialysis.

Most AV access grafts are tubes made of a plastic called polytetrafluoroethylene (PTFE). These grafts can first be used for dialysis about two weeks after they are implanted; this time is needed to allow the graft to heal into the surrounding tissue. If dialysis is needed during these two weeks, it is common to use a catheter placed through the skin in the neck into a vein in the chest to provide the needed blood access. Figure 2 diagrams a common temporary catheter placement.

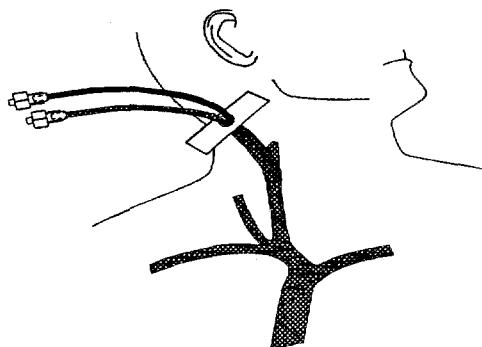


Figure 2

87

Temporary catheters also have complications associated with their use, which your physician can discuss with you.

Your physician has determined that the combination of a standard PTFE AV access graft and a temporary catheter is not the best option to support your need for long-term blood access for dialysis. Instead, your physician would like to use the Perma-Seal Graft.

Your physician's reasons might include the need for immediate dialysis but the inability to use a temporary catheter, or evidence that a temporary catheter would be hazardous in your case. Be sure to discuss and understand the reasons for your physician's recommendation.

Unlike conventional grafts made of PTFE, the Perma-Seal graft is made of solid silicone rubber. This material and design give the Graft self-sealing properties; see the picture on the front of this brochure. Self-sealing properties allow the Graft to be used for dialysis access immediately after implantation. They also help stop bleeding after the needles are taken out of the Graft when a dialysis session is over.

The Perma-Seal Graft has some disadvantages, too. In a clinical trial, patients with Perma-Seal Grafts had similar types of complications as seen with standard PTFE grafts. However, the Perma-Seal Graft patients had more of these complications: 3.7 each year, compared with 1.7 each year for patients with standard Teflon grafts. The table in this brochure lists the types and frequencies of complications seen in the clinical trial. Your physician can discuss with you the types of complications you may experience, and how they may be treated.

Be sure to follow your physician's instructions for care of the Graft until healing of the surgical wound, including:

- Keep the arm elevated
- Keep the incision area clean and dry

Also follow the instructions of the medical personnel at the dialysis clinic where the Graft will be used for dialysis access, including:

- Do not put any pressure on the arm which may stop blood flow in the Graft
- Do not use the Graft for other access purposes such as blood tests, drug injections, etc.
- Wash the arm before each dialysis session

Seek a physician's care if you have any of these:

- Swelling, redness, pus drainage, or fever
- A spreading bruise at the dialysis needle site
- A cold, numb, or weak hand

Complications:

A clinical study was conducted to compare performance of the Perma-Seal Graft to conventional PTFE grafts when used for dialysis access. Causes of death reported for Perma-Seal patients included sepsis, cardiac arrest, elective discontinuation of dialysis, cardiomyopathy, coronary artery disease, heart failure, multiple system failure, ruptured gall bladder, intracranial bleeding, and uncontrolled bleeding through a cut temporary catheter. No deaths were reported to be caused by the Perma-Seal Graft. Causes of death reported for study patients treated with PTFE grafts were similar. Other complications reported for study patients treated with the Perma-Seal Graft included aneurysm, hematoma, infection, pseudoaneurysm, surgical graft revision, skin erosion, steal syndrome, thrombectomy, and thrombosis.